REMARKS

Claims 31, 32, and 43-49 are pending in the application and under active consideration. Claims 48 and 49 have been canceled without prejudice or disclaimer. Claims 31, 32, 44, and 47 have been amended to further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested.

Claims 31 and 32 have been amended to recite glycoconjugates produced by methods comprising the step of covalently attaching a C3-C16 long-chain aliphatic lipid to the nonreducing end of the MenB OS. Support for these amendments can be found in the specification, for example, at page 14, line 16 through page 16, line 33, which describe methods of preparing glycoconjugates with covalently attached lipids. Accordingly, the specification provides adequate support for these amendments.

Claims 31, 32, 44 and 47 have been amended to remove the term derivative. This amendment addresses the rejection under 35 U.S.C. § 112, second paragraph. Applicant is amending these claims solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

Claims 31, 32 and 47 have been amended to recite "degree of polymerization (Dp)." Support for these amendments can be found in the specification, for example, at page 4, line 18, which describes DP as an abbreviation for "degree of polymerization." These amendments address the rejection under 35 U.S.C. § 112, second paragraph on the grounds that the full terminology for the abbreviation is required to appear in the claims. Applicant is amending these claims solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

To expedite prosecution, claims 31 and 32 have been amended to recite "the reducing end" as an oligosaccharide has only one reducing end.

To expedite prosecution, claims 31 and 32 have been amended as suggested by the Examiner to recite "the single end-activated MenB OS" to correct antecedent basis.

To expedite prosecution, Applicant has amended claims 31 and 32 to recite "a substantially homogeneous sized group of MenB OS" to further clarify the intended subject matter of the claimed invention. Support for these amendments can be found in

the specification, for example, at page 11, lines 16-30. Accordingly, the specification provides adequate support for these amendments.

To expedite prosecution, claims 31 and 32 have been amended to remove the term moieties. These amendments address the rejection under 35 U.S.C. § 112, second paragraph. Applicant is amending these claims solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

Applicant reserves the right to prosecute non-elected subject matter in subsequent divisional applications.

Objections to the Title

The title has been revised to reflect the fact that the claims are drawn to *Neisseria meningitides* glycoconjugates and methods of producing them. Withdrawal of the objection to the title is therefore respectfully requested.

Objections to the Specification

Priority

The priority information has been revised as suggested by the Examiner to include a reference to the issued patent, U.S. Patent No. 6,638,513. Withdrawal of the objection to the Specification is therefore respectfully requested.

Trademarks

The specification has been amended to properly recite trademarks with marks capitalized and accompanied by generic terminology. Withdrawal of the objection to the Specification is therefore respectfully requested.

Figures

The specification has been amended on page 6, line 21 to correct the recitation of the figures, Figures 5A and 5B. In addition, Applicant has amended the paragraph beginning on page 28, line 15 to replace references to Figure 1 with references to Figures 5A and 5B. The chromatograms discussed in the paragraph clearly refer to Figures 5A

and 5B and not to Figure 1. Therefore, this amendment is necessary to correct the inadvertent error by Applicant. Entry of this amendment and withdrawal of the objection to the Specification is respectfully requested.

Double Patenting Rejection

Claims 31, 32, and 43-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,638,513. Applicant requests that the requirement for submission of a Terminal Disclaimer with respect to U.S. Patent No. 6,638,513 be held in abeyance until there is an indication of allowable subject matter in the present application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 31, 32, and 43-49 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, pages 4-5). Claims 48 and 49 have been canceled; therefore, the rejection with respect to these claims is moot.

(a) The Examiner alleges that "[c]laims 31, 32, 44 and 47-49 are indefinite and confusing in the recitation 'derivatives' or 'derivative', because it is unclear what is encompassed in this recitation" (Office Action, page 4). Applicant notes that the definition of the term derivative appears in the claims, i.e., a MenB OS in which sialic acid residue N-acetyl groups are replaced with N-acyl groups (claim 31) or N-propionyl groups (claim 32). Nevertheless, in order to expedite prosecution, claims 31, 32, 44 and 47 have been amended to remove the term derivative(s).

(b) The Examiner alleges that "[c]laims 31, 32 and 47 are vague and indefinite because it is unclear what the abbreviation 'Dp' stands for" (Office

Action, page 4). To expedite prosecution, claims 31, 32 and 47 have been amended to indicate that Dp is an abbreviation for degree of polymerization.

(c) The Examiner alleges that "[c]laims 31 and 32 are vague and indefinite in the recitation 'a reducing end of the derivatives' as opposed to --the reducing end of the derivatives--" because it is unclear whether the derivatives comprise more than one reducing end (Office Action, page 4). To expedite prosecution, claims 31 and 32 have been amended to recite "the reducing end" as an oligosaccharide has only one reducing end.

(d) The Examiner alleges that "[c]laims 31 and 32 are vague and indefinite in the limitation: 'the end-activated MenB OS derivatives' (see part d of the claims)" (Office Action, page 4). To expedite prosecution, claims 31 and 32 have been amended as suggested by the Examiner to recite "the single end-activated MenB OS" to correct antecedent basis.

(e) The Examiner alleges that "[c]laims 31 and 32 are vague and indefinite in the limitation: 'substantially homogeneous' (see parts b and d of the claims), because it is unclear what is encompassed in this phrase. The specification does not provide a standard for ascertaining the requisite degree of homogeneity that qualifies as substantial homogeneity" (Office Action, page 5). Applicant respectfully disagrees and traverses the rejection.

The specification describes the preparation of "substantially homogeneous" populations of MenB OS, as follows:

> A heterogenous population of high molecular weight MenB PS derivative molecules is thus obtained. Previous methods have used such heterogenous high molecular weight derivatives in glycoconjugate preparations, where the derivatives are subjected to controlled periodate oxidation to create terminal aldehyde group at the non-reducing end for conjugation (through the aldehydric group at the non-reducing end of the polysaccharide) to a protein carrier. **However, in the practice of the**

> **present invention, the above-described N-acylated MenB polysaccharide derivatives are fragmented and then size-fractionated to provide a substantially homogeneous population of intermediate "sized" MenB oligosaccharide fragments for use in preparing glycoconjugates.** (Specification, page 11, lines 16-30; Emphasis added.)

Thus, a "substantially homogeneous" group of MenB OS, as recited in claims 31 and 32, is a group of MenB OS obtained by size-fractionation such that the average degree of polymerization (Dp) of the oligosaccharides is within the specified range recited in the claims. Methods of obtaining such a "substantially homogeneous" population are described in the specification, for example, at page 12, lines 1-19 and Example 5, at pages 34-36.

To expedite prosecution, Applicant has amended claims 31 and 32 to recite "a substantially homogeneous sized group of MenB OS" to further clarify the intended subject matter of the claimed invention. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph on this basis is respectfully requested.

(f) The Examiner alleges that "[c]laims 31 and 32 are vague and indefinite in the limitation: 'MenB OS moieties' (see last lines(s)) and 'MenB OS derivatives', because it is unclear how one differs from the other structurally, conformationally, or scope-wise" (Office Action, page 5). To expedite prosecution, claims 31 and 32 have been amended to remove the term moieties.

(g) The Examiner alleges that "[c]laims 47-49 have improper antecedence in the limitation: 'the MenB OS derivative'. Claims 47-49 depend from claim 31 or 32, which recite 'MenB OS' derivatives' as opposed to a 'MenB OS derivative'" (Office Action, page 5). Claims 48 and 49 have been canceled; therefore, the rejection with respect to these claims is moot. To expedite prosecution, claims 31, 32, and 47 have been amended to remove the term derivative. The term MenB OS has proper antecedent basis.

(h) The Examiner alleges that "[c]laim 31 is vague and indefinite in the recitation 'a carrier molecule', because it is unclear what is encompassed in this limitation" (Office Action, page 5). Applicant respectfully disagrees and traverses the rejection on the following grounds.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983). Claim 31 meets the legal standards required by 35 U.S.C. § 112, second paragraph.

The term "carrier molecule" is described in the specification as follows:

> Each of the above-described glycoconjugates are prepared using **carrier molecules that will not themselves induce the production of harmful antibodies. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles.** Preferably, the sized MenB OS derivative fragments of the present invention are conjugated to a bacterial toxoid, such as but not limited to a toxoid from diphtheria, tetanus, cholera, etc. In particular embodiments, the oligosaccharide fragments are coupled to the CRM_{197} protein carrier. The CRM_{197} carrier is a well-characterized non-toxic diphtheria toxin mutant that is useful in glycoconjugate vaccine preparations intended for human use. Bixler et al. (1989) Adv. Exp. Med. Biol. 251:175, Constantino et al. (1992) Vaccine. In other embodiments, the MenB OS derivative fragments are coupled to protein carriers known to have potent T-cell epitopes. Exemplary carriers include, but are not limited to, Fragment C of tetanus toxin (TT), and the Class 1 or Class 2/3 OMPs of N. meningitidis. Such carriers are well known to those of

ordinary skill in the art. (Specification at page 17, line 25 through page 18, line 13; Emphasis added.)

Therefore, a person of skill in the art would **reasonably** understand the metes and bounds of the phrase "carrier molecule" **in the context of the claims**. Therefore, withdrawal of the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

(i) The Examiner alleges that "[c]laims 43-49 which depend directly or indirectly from claim 31or claim 32, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim" (Office Action, page 5). Applicant respectfully traverses the rejection on this basis for at least the reasons stated above.

For at least the above reasons, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 31, 32, and 43-47 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by the reference of Jennings et al. (U.S. Patent No. 5,811,102). In particular, the Office Action alleges that Jennings et al. teach "a glycoconjugate comprising Neisseria meningitides serogroup B capsular polysaccharide fragment derivatives (i.e., oligosaccharide derivatives) in which sialic acid N-acetyl groups are replaced with N-propionyl groups, wherein such oligosaccharide derivatives are covalently attached to a carrier molecule, such as, tetanus toxoid (see Example 8)" (Office Action, page 6). The Office Action further notes that the "[i]nstant claims are product-by-process claims and are not limited to the manipulations of the recited steps, but only the structure implied by the steps" and that "Applicant has not shown that the alleged differences in the process result in a product that is structurally different from the product of the prior art." Applicant respectfully traverses the rejection under 35 U.S.C. § 102(e) on the following grounds.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicant respectfully submits that the reference of Jennings et al. does not teach all aspects of the Applicant's invention as now claimed, either explicitly or implicitly.

Jennings et al. does not disclose a glycoconjugate comprising a covalently attached C3-C16 long-chain aliphatic lipid, as recited in claims 31 and 32, as currently amended. Therefore, not all the limitations of the claims are taught by the Jennings et al. reference and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 48 and 49 are rejected under 35 U.S.C. § 103 as being unpatentable over the reference of Jennings et al. U.S. Patent No. 5,811,102 in view of the references of Sato et al. (1995) J. Biol. Chem. 270:18923-18928 and Staveski et al. U.S. Patent No. 5,354,853. Claims 48 and 49 have been canceled; therefore, the rejection with respect to these claims is moot. However, claims 31 and 32, as amended, recite embodiments of the invention originally claimed in claims 48 and 49. Applicant will therefore address the rejection under 35 U.S.C. § 103 with respect to claims 31 and 32 and their dependent claims accordingly.

In particular the Office Action alleges:

> Since the techniques of conjugating lipids to a saccharide or specifically to an oligosaccharide of alpha (2->8)-linked polysialic acid are well known in the art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to attach Staveski's or Sato's phospholipid, phosphatidylethanolamine, to Jennings' (102) N-propionylated serogroup B meningococcal capsular oligosaccharide glycoconjugate using Staveski's or Sato's method to produce the glycoconjugate of the instant invention, with a reasonable expectation of success. Given that lipidation of oligosaccharides is routinely practiced in the art for production of liposomes as taught by Staveski et al., one of skill in the art would have been motivated to produce the instant invention for the expected benefit of using Jennings' (102) conjugate, advantageously, as a liposome preparation, for the purpose of further increasing the immunogenicity of the conjugate.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on appliant's disclosure." M.P.E.P. § 706.02.

Applicant submits that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combination is based on impermissible hindsight reconstruction.

Jennings et al. does not teach or disclose a glycoconjugate comprising a covalently attached C3-C16 long-chain aliphatic lipid, as acknowledged by the Examiner. In addition, the primary reference does not disclose the preparation of glycoconjugates having substantially homogenous sized MenB OS wherein the average degree of polymerization of the MenB OS is 10-20 as recited in claim 31 or 12-18 as recited in claim 32. The secondary references of Sato et al. and Staveski et al. do not cure the deficiencies of Jennings et al.

The reference of Sato et al. describes some oligosaccharide-lipid conjugates; however, the oliosaccharides used in the conjugates are structurally different from MenB OS. Sato et al. fails to describe glycoconjugates comprising MenB OS, nor provides any incentive for using MenB OS. Therefore, the teachings of Sato et al. are not applicable to the present invention. Further, the reference of Staveski et al. discloses phospholipid-saccharide conjugates and their use to produce liposomes; however, does not provide any incentive to use the claimed MenB OS glycoconjugates, as claimed.

Thus, the references do not disclose or suggest all the limitations of the present invention, and the Examiner has not met the burden of establishing a *prima facie* case of obviousness. In the absence of some teaching or suggestion in the cited references concerning the compounds and compositions of the present invention, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600

(Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least the above reasons, withdrawal of the rejection under 35 U.S.C. § 103 (a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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